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preferentially in the areas of the hypothalamus responsible for the regulation of body weight and energy balance.

Remarks

Restriction Requirement

Applicants greatly appreciate the examiner's review of all pending claims 1-15 in this application.

Rejection under 35 U.S.C. §103

Claims 7, 8 and 9 were rejected under 35 U.S.C. §103 as obvious over Thomsen, et al., Proc. Natl. Acad. Sci. USA 81, 659-663 (1984), Boshart, et al., Cell 41, 521-530 (1985) and U.S. Patent No. 5,486,599 to Saunders. This rejection is respectfully traversed if applied to the claims as amended.

Please note: the U.S. patent cited by the examiner does not appear to have been made of record on either the PTO-892 nor the PTO 1449 forms which have been submitted, nor was a copy provided to applicants.

Claims 7-9 are drawn to constructs for making a transgenic animal comprising

a promoter (in claim 8, wherein the promoter is the cytomegalovirus promoter or a functional portion thereof including the intermediate/early enhancer.)and

a nucleic acid molecule encoding a syndecan (claim 9, wherein the syndecan is syndecan-1),

wherein the syndecan is preferentially expressed in the hypothalamus.

The claims have now been amended to include the language at page 4, lines 25-27 and page 28, lines 2-4, requiring expression in those areas of the hypothalamus responsible for the regulation of body weight and energy balance. Dr. Reizes' Declaration under 37 C.F.R. §1.132 provides additional proof that the expression is specific for the hypothalamus and more particularly, specific to those areas of the hypothalamus responsible for the regulation of body weight and energy balance.

The art cited by the examiner discloses the CMV promoter and syndecan-1 gene.

This is not sufficient. A rejection under §103 requires motivation to combine with an expectation of success. The syndecan encoded by the construct must by definition be preferentially expressed in the areas of the hypothalamus involved in weight regulation.

None of the art provides any indication that the combination of a CMV promoter and syndecan gene would result in preferential expression in the hypothalamus. Moreover, the examiner's own statement is indicative that the art in fact teaches away from such a conclusion by calling the promoter an ubiquitous promoter, and by the reference to Boshart, et al., that "hCMV enhancer shows little cell type or species preference."

In summary, the art does not disclose that the CMV promoter, or any other promoter, would result in preferential expression within the hypothalamus, much less within regions involved with weight regulation.

Rejections under 35 U.S.C.§112

Claims 1-15 were rejected under 35 U.S.C. §112 as not enabled. Claims 1-6 and 10-15

were rejected as indefinite. These rejections ares respectfully traversed if applied to the amended claims.

Claims 1 and 10 were objected to on the basis that the binding function is inactivated and to what extent binding is disrupted. The claims have been amended to define the animals as genetically engineered to express a syndecan which binds to the MC4-R which are characterized by an obese phenotype. Support for these amendments is found, for example, at page 16, lines 26-32.

The claims were also rejected for animals other than mice on the basis that the animals must be produced using embryonic stem cell technology. The claimed animals can all be made by microinjection. References for microinjection into species of animals other than mice are cited in the application and such techniques were well known as of the filing date of this application.

The claims were also rejected on the basis that the melanocortin 4 receptor ligand was not known, nor the region of the protein which binds to the native ligand. This rejection is mooted by the amendments to the claims. However, the statements are not accurate. Two papers and two reviews are enclosed which describe the melanocortin receptors, their ligands (aMSH) and the agouti proteins), and their role in skin pigmentation and obesity:

Lu, et al., "Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor" Nature 371, 799-802 (1994); Ollmann, et al., "Antagonism of Central Melanocortin Receptors in Vitro and in Vivo by Agouti-Related Proteins" Science 278, 135-138 (1997); Yen,

et al., "Obesity, diabetes, and neoplasia in yel A^{vy}/- mice: ectopic expression of the agouti gene" FASEB J. 8, 479-488 (1994); and Cone, et al., "The Melanocortin Receptors: Agonists, Antagonists, and the Hormonal Control of Pigmentation" Recent Prog. Hormone Res. 51, 287-318 (1996).

The examiner appears to question that the data in the application shows that syndecan binds to the MC4-R, and that this binding affects the body weight. Rather than debate the point, the objected language has been removed, since the claims now refer to the animals having an obese phenotype and the data does show that this is a result of expression of the syndecan.

With regard to the syndecans *per se*, and the examiner's objection to generalizing to more than one syndecan (syndecan-1) and one animal species, enclosed are one article and two reviews which discuss the importance of the HSPGs and their functional redundancy at the cell surface. It is important to point out that the functional part of these molecules is their heparan sulfate chanins. The core proteins are thought to be important for localization of the heparan sulfate to the cell surface or the extracellular milleu. This is further supported by the papers attached to Dr. Reizes' Declaration and the data showing upregulation of syndecan-3 in the hypothalamus of wild-type mice when they were fasted.

It is believed that the rejections relating to indefiniteness have been addressed by the foregoing amendments.

Allowance of all of claims 1-15, as amended, is earnestly solicited in view of the foregoing remarks and accompanying Declaration. All claims as pending upon entry of this

amendment are attached in an appendix for the convenience of the Examiner.

Respectfully submitted,

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I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Date: April 9, 1999

Jean Hicks